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Metformin Associates With Aggressive Features of Endometrial Cancer in Women With Type 2 Diabetes

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Abstract. *Background/Aim: Preclinical studies on metformin use and endometrial cancer have been promising but epidemiological studies have reported variable results. This study aimed to assess if metformin use is associated with endometrial cancer aggressiveness and survival in women with type 2 diabetes (T2D). Patients and Methods: This retrospective hospital-based cohort consisted of women with T2D who were treated for endometrial cancer at the Oulu University Hospital, Finland, between 2007 and 2014. Results: The sample size was 121 patients: 58 metformin users and 63 metformin non-users. Intriguingly, type 2 histology, deep myometrial invasion and the presence of lymphovascular invasion were more common in the metformin user group. However, metformin use showed no association with overall survival and progression-free survival. Conclusion: Metformin use was associated with poorer prognostic factors in endometrial cancer patients with T2D.*

Endometrial cancer is the fifth most common cancer type in women worldwide (1). The age-standardised incidence of endometrial cancer is rising mostly due to lifestyle factors such as obesity (2). Type 2 diabetes (T2D) is the most rapidly increasing chronic disease globally, and has been estimated that more than 460 million adults have diabetes, with more than 90% of them suffering from T2D (3). Although, T2D and endometrial cancer share some risk factors, diabetes itself seems to be an independent risk factor for endometrial cancer (4).

The majority of endometrial cancers are diagnosed at an early stage (5). Regarding early endometrial cancer, the five-year survival rate is 95% but decreases to as low as 16% in stage IV cancer (6). Endometrial cancers are traditionally classified as type 1 and type 2 cancers and type 1 endometrial cancers are more frequent and have a better prognosis than type 2 cancers (7). Type 2 endometrial cancers are poorly differentiated and are more commonly identified by their deep invasion into the myometrium, higher frequency in pelvic lymph node metastases and decreased sensitivity to progesterone (7).

Metformin is the main first-line therapy for T2D (8). In the treatment of hyperglycaemia, metformin reduces the hepatic glucose outlay, increases peripheral tissue sensitivity and stimulates glucagon-like peptide-1 secretion (9). Metformin is also weight neutral (9) and has favourable effects on cancer cells both directly and indirectly (10). It sensitises tissues to insulin, decreases hepatic gluconeogenesis and reduces circulating insulin levels, and these effects indirectly lead to both reduced tyrosine kinase activation and phosphatidylinositol-3-kinase signalling (10).

Metformin has shown multiple molecular mechanisms in endometrial cancer cells (11). In *in vitro* studies, metformin seems to inhibit the proliferation and invasion of both endometrioid and non-endometrioid endometrial cancer cells (12-14). Metformin activates AMP-activated protein kinase and this leads to inhibition of mammalian target of rapamycin (15). In addition, it induces apoptosis (15), inhibits oxidative phosphorylation at the mitochondrial level and inhibits epithelial-to-mesenchymal transition (11). Metformin has been shown to synergize with chemotherapy and progesterone treatment in endometrial cancer cells (11). In addition, a

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meta-analysis of previous epidemiological studies indicated that metformin users have a better overall survival (OS) rate and a decreased risk of endometrial cancer recurrence (16).

This retrospective study was aimed to explore whether metformin users diagnosed with endometrial cancer have a less aggressive cancer phenotype or better survival rate in a hospital-based cohort with comprehensive clinical data.

Patients and Methods

Patients. The data of the patients included in this study were obtained from Oulu University Hospital records. These records included information on the patients' age at the time of diagnosis, parity, antidiabetic medication (ADM) and body mass index (BMI). In addition, we obtained information on endometrial cancer such as stage, histology, myometrial invasion, lymphovascular invasion (LVI), oestrogen receptor (ER) status, residual tumour after the surgery, progression and death from hospital records. All endometrial cancer diagnoses were based on histology. Stages were rechecked and fitted to the current International Federation of Gynaecology and Obstetrics (FIGO) stage (17). Endometrial cancers were categorised as type 1 and type 2 cancers according to their histology, so that grade 1 and grade 2 endometrioid endometrial cancers (n=63 and n=27, respectively) and mucinous (n=1) cancers were labelled as type 1 cancers, whereas grade 3 endometrioid (n=11), serous (n=13), clear cell (n=1), mixed high grade (n=3), undifferentiated endometrial cancers (n=1) and carcinosarcomas (n=1) were classified as type 2 cancers.

Classification of patients to metformin users and non-users was based on the ADM being used at the time of endometrial cancer diagnosis. Patients were classified as metformin users if they had used metformin alone or combined with some other oral ADMs. On the other hand, the patients were categorised as metformin non-users if they used only other forms of oral ADMs, insulin (alone or combined with metformin and/or other oral ADMs) or did not use any ADM.

The follow-up of the patient began at the time the endometrial cancer surgery was done, except for patients who were not eligible for surgery (n=14). In those cases, the start of the follow-up was the date of diagnosis from the endometrial sample. Follow-up ended at the time of death or closure of the follow-up period (7th August 2018). The median follow-up time was 65 months.

Statistical analysis. Statistical analysis was performed with IBM SPSS Statistics, version 25 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism, version 8.0.2 (GraphPad Software, San Diego, CA, USA) software. Comparisons between two medication groups were evaluated using the two-sample *t*-test and Mann-Whitney *U*-test for continuous variables and Pearson chi-square and Fisher's exact test for categorical variables. FIGO stage was distributed into two categories – early or advanced. Early stage included FIGO stages I A and I B, while advanced stage included stages II, III and IV. Kaplan-Meier curves with the log-rank test were applied to the survival analysis. OS was calculated from the time of surgery or cancer diagnosis to the time of death. Progression-free survival (PFS) was calculated from the time of the surgery or cancer diagnosis to the date of radiological progression. Cox regression analysis was applied for multivariate analysis, where the traditionally most important prognostic factors – age, histology and the stage of endometrial cancer – were included along with metformin use in the model. In all statistical analyses, *p*-values <0.05 were considered statistically significant.

Results

Patient and tumour characteristics. There were 121 women with T2D diagnosed with endometrial cancer between 2007 and 2014 at Oulu University Hospital in Finland (Figure 1). The metformin user group had 58 women, of which 35 were using metformin alone, while 23 were using metformin combined with some other oral ADMs. The metformin non-user group had 63 patients – of which 37 were insulin users, 8 were using some other oral ADMs and 18 were not using any ADMs.

The mean age for endometrial cancer diagnosis was 70.5 years among the metformin users and 71.2 years among the metformin non-users ($p=0.67$) (Table I). The metformin non-users were slightly more obese than the metformin users, as median BMI was 33.0 in the metformin users and 36.0 in the metformin non-users ($p=0.11$). Parity and the presence of fatty liver were similar in both groups.

There were more adverse prognostic factors in the metformin user group (Table II). Intriguingly, type 2 histology ($p=0.018$) and the presence of LVI ($p=0.04$) and deep myometrial invasion ($p=0.035$) were more common in the metformin user group (Table II). There was also a trend of more advanced-stage endometrial cancers in the metformin user group ($p=0.07$). However, there were no statistically significant differences in tumour size ($p=0.61$), peritoneal cytology ($p=0.98$) and ER status ($p=0.33$) between the medication groups. In addition, residual tumour after surgery ($p=0.12$), the number of patients who received adjuvant treatment ($p=0.12$) and the number of patients who were not eligible for operation ($p=0.123$) did not show statistically significant differences between metformin users and non-users.

Overall survival. As expected, univariate analysis showed OS was worse in patients with type 2 endometrial cancers than in patients with type 1 ($p=0.0000018$) (Figure 2). Similarly, OS was worse in patients with advanced-stage cancer ($p=0.000013$), patients ≥65 years of age ($p=0.006$) and patients with deep myometrial invasion ($p=0.0000093$). ER status ($p=0.79$) and BMI ($p=0.82$) showed no association with OS.

Univariate analysis of the whole cohort revealed that metformin use had no association with OS ($p=0.67$). Furthermore, metformin use was not associated with OS when assessed separately in subgroups of type 1 histology ($p=0.19$), type 2 histology ($p=0.21$), superficial myometrial invasion ($p=0.27$), deep myometrial invasion ($p=0.57$), presence of LVI ($p=0.31$), early-stage cancer ($p=0.33$),

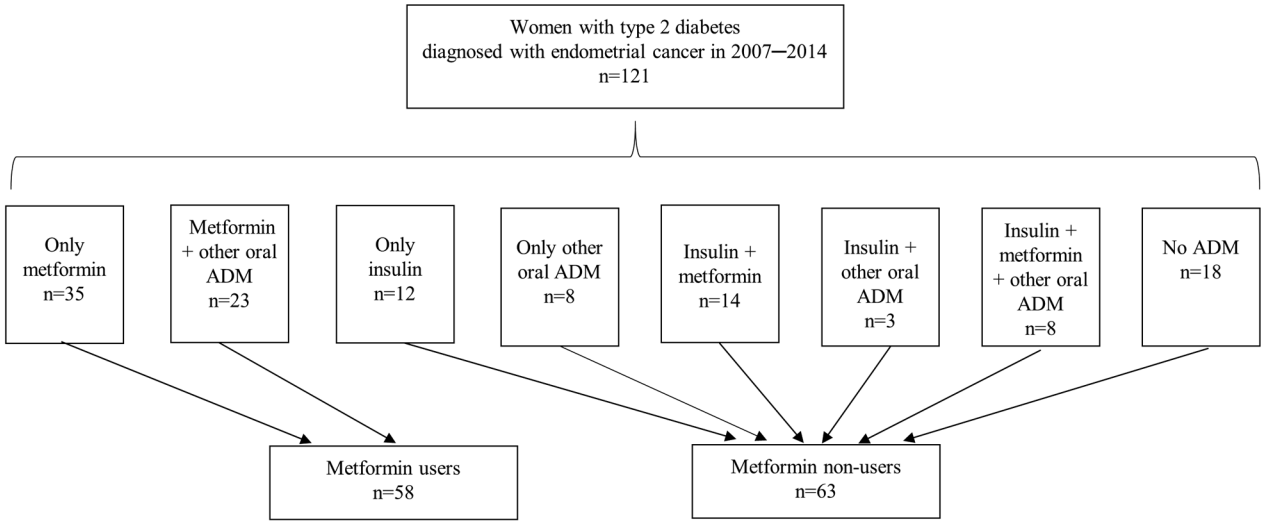

Figure 1. *Distribution of antidiabetic medication (ADM).*

advanced-stage cancer (p=0.64), ER-negative endometrial cancers (p=0.87), ER-positive endometrial cancers (p=0.57), higher BMI class (p=0.22) and older patients (p=0.35). Similarly, Cox regression analysis showed that metformin use was not associated with OS after adjusting for histology type, stage and patient's age [Hazard ratio (HR)=0.86, 95% confidence interval (CI)=0.41-1.79] (Table III). In addition, advanced stage and type 2 histology were associated with poorer OS in the patients ≥65 years old subgroup while advanced stage of cancer was only associated with poorer OS in the patients of type 2 histology subgroup.

Progression-free survival. Similar with OS, PFS was worse in type 2 histology (p=0.000004), more advanced stage (p=0.000000000001) and deep myometrial invasion (p=0.0003) in univariate analysis (Figure 3). However, older age (p=0.11), higher BMI (p=0.54) and ER negativity (p=0.36) of the tumour showed no association with PFS.

In the whole cohort, metformin use was not associated with PFS (p=0.1) in univariate analysis. However, metformin use was associated with poorer PFS in type 2 histology (p=0.015). In addition, metformin use is associated with poorer PFS in older patients (p=0.015). Nevertheless, metformin use was not linked with PFS when separately assessed in subgroups of type 1 histology (p=0.2), superficial myometrial invasion (p=0.18), deep myometrial invasion (p=0.5), higher BMI class (p=0.091), presence of LVI (p=0.1), ER-positive cancer (p=0.26), ER-negative cancer (p=0.06), early-stage cancer (p=0.44) or advanced-stage cancer (p=0.51). However, in the Cox regression analysis, the advanced stage was the only factor that was associated with poorer PFS after adjusting for metformin use, histology and age (Table III). When Cox regression analysis was done only among patients with either type 2 histology or among those ≥65 years age, in both of these analyses, only advanced stage was an adverse prognostic factor for PFS.

Discussion

Metformin has shown various anti-cancer effects on endometrial cancer cells in preclinical studies. In addition to its growth inhibitive effect (12), metformin seems to sensitise endometrial cancer cells to both chemotherapy (18) and progestins (19).

In a small clinical study, preoperative use of metformin was associated with lower cell proliferation, Ki-67 expression, in endometrial cancer (20). Contrary to this finding, a recent phase III study did not find reduced tumour proliferation in endometrial cancer among metformin users (21). Metformin has also been found to prevent tamoxifen-associated endometrial proliferative changes in breast cancer patients (22).

Thus, contrary to most previous results, in the current hospital-based cohort study, metformin use at the time of endometrial cancer diagnosis in women with T2D was found to be associated with poorer prognostic factors, but no associations with either OS or PFS were found. Although the majority of previous retrospective cohort studies have indicated that metformin use is associated with better survival in patients with endometrial cancer, this evidence is not robust. Few studies have observed a better OS among metformin users with endometrial cancer, including all histological endometrial cancer types (23, 24) while better OS was only noted in non-endometrioid subtype in one study

Table I. *Patient characteristics in the two medication groups: metformin users and non-users. STD: Standard deviation, BMI: body mass index, WPRT: whole-pelvic radiation therapy. Significant p-Value is given in bold.*

	Metformin users (n=58)	Metformin non-users (n=63)	*p*-Value
Age at diagnosis (years)			
Mean	70.5	71.2	0.667
STD	8.56	9.36	
Min	51	51	
Max	88	88	
Age group at diagnosis			
<65 years	19	14	0.194
≥65 years	39	49	
BMI (kg/m^2)			
Median	33.0	36.0	0.106
Range	19-55	22-65	
Missing	4	6	
BMI class (kg/m^2)			
<35	34	21	**0.008**
≥35	21	36	
Missing	4	6	
Menopause age			
Premenopausal	2	3	0.479
Under age 50	6	9	
50-53 years old	24	26	
≥54 years old	18	11	
Missing	8	14	
Fatty liver			
Yes	21	21	0.315
No	16	25	
Missing	21	17	
Parity			
Median	2	2	0.317
Range	0-9	0-13	
Adjuvant treatment			
None	27	31	0.307
WPRT	11	11	
Chemotherapy	13	6	
Vaginal brachytherapy	4	8	
Intracavitary radiation	2	6	
Hormonal treatment	1	1	

Table II. *Tumour characteristics in the two medication groups: metformin users and non-users. ER: Oestrogen receptor. Significant p-Values are given in bold.*

	Metformin users (n=58)	Metformin non-users (n=63)	*p*-Value
Histology			
Type 1	38	53	**0.018**
Type 2	20	10	
Stage			
Early (IA-IB)	37	47	0.07
Advanced (≥II)	19	11	
Missing	2	5	
Deep myometrial invasion			
Yes	26	15	**0.035**
No	28	38	
Missing	4	10	
Lymphovascular invasion			
Yes	24	12	**0.04**
No	31	37	
Missing	3	14	
ER status			
Positive	49	51	0.33
Negative	7	12	
Missing	2	0	
Peritoneal cytology			
I-II	41	42	0.976
III	2	2	
IV	3	2	
V	2	2	
Missing	10	15	
Residual tumour after surgery			
No	49	52	0.118
Yes	4	0	
No operation	4	10	
Missing	1	1	

(25). In contrast to this, a lower risk for recurrence has been reported in type 1 endometrioid cancers in metformin users in another study (26).

On the other hand, similar to our study, some studies have not observed any association between metformin use and survival in patients with endometrial cancer (27-29). In our previous register-based studies, metformin use was not associated with lower endometrial cancer-related mortality in either endometrioid or non-endometrioid histologies, but metformin users had lower mortality from other causes among endometrioid endometrial cancer patients (30, 31).

In a previous meta-analysis, no association between metformin use and endometrial cancer risk was seen (16); however, histological subtypes were not analysed separately. No association between metformin use and non-endometrioid endometrial cancer incidence was seen in our previous study (31), rather, metformin ever-use was linked with increased risk for endometrioid endometrial cancer among the patients compared to those who had never used metformin (32).

In our present study, metformin use was associated with poorer prognostic factors, which may interfere with the survival results. The most established negative prognostic factors for endometrial cancer, advanced-stage cancer and type 2 histology were also the most important factors impacting on survival in our study, suggesting that the cohort was representative. However, analysing histological subtypes separately is not reliable due to the small amount of type 2 cancers, particularly the non-endometroid type (n=30). In

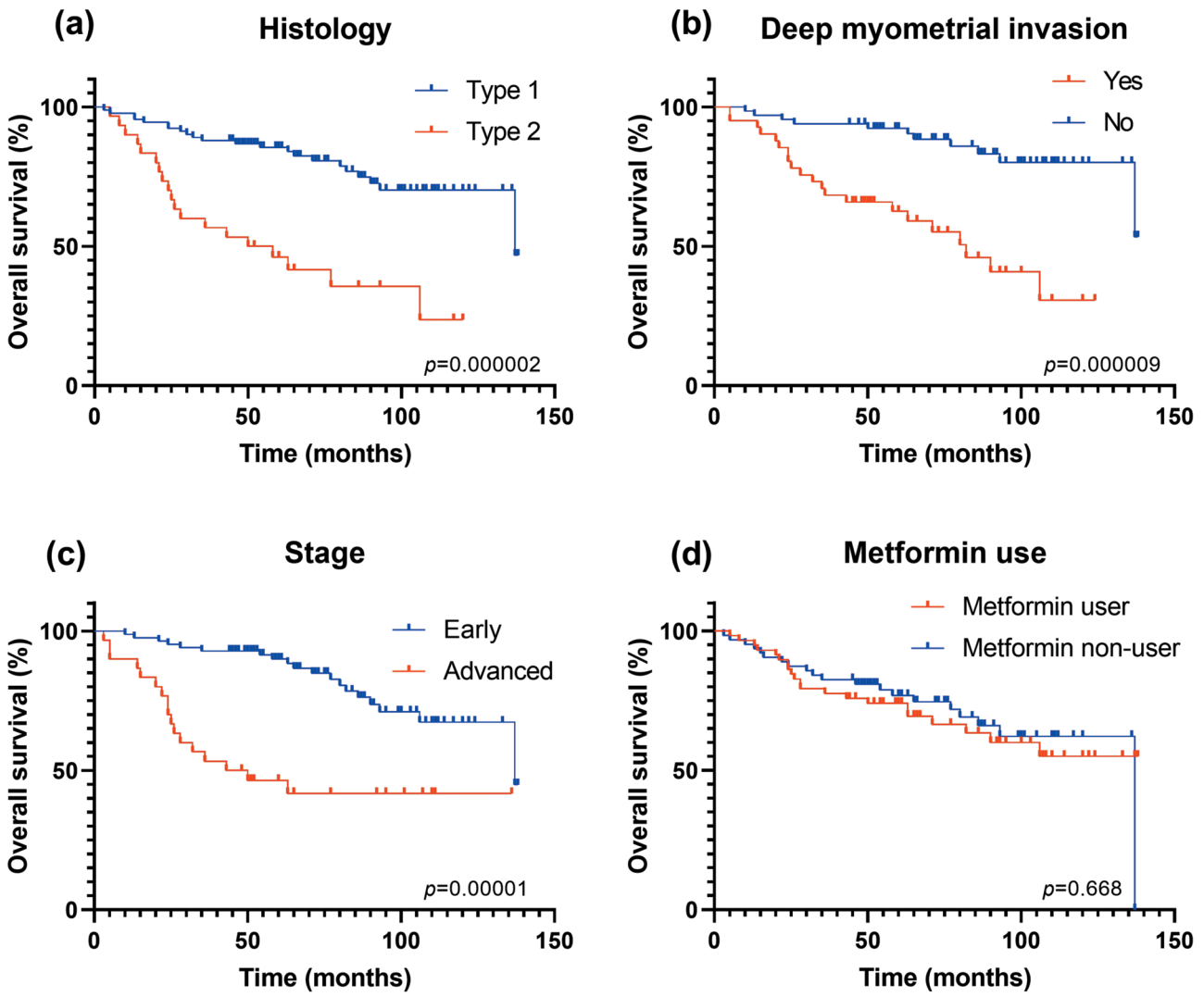

Figure 2. *Kaplan-Meier curves demonstrate associations between (a) histology, (b) myometrial invasion (c) stage or (d) metformin use and overall survival.*

previous studies, metformin use was not linked to more aggressive histology or more advanced stage (23-26, 28, 29). However, similar to our study, metformin users were younger in some of the previous studies (24, 30), while others have not reported such a difference (23, 25, 26). In some studies, metformin users had higher BMI than metformin non-users, which is in contrast to our findings (26, 28, 29). Also, a better OS in metformin users with higher BMI has been reported (28).

The strengths of this study include reliable data on patient and cancer characteristics, and, over five-year median follow up. We had the patients' data at the time of endometrial diagnosis, such as BMI and parity, and cancer-related data such as ER status and myometrial invasion, which are usually missing in register-based studies. On the other hand, as a limitation, information on the cause of death was not available and the sample size was not very extensive due to the single-institution based records. The information on duration and severity of diabetes and dose of the used medications were lacking, which might lead to bias, as longer duration of diabetes is associated with, for example, increased cardiovascular mortality (33). We presumed continuous ADM exposure after the endometrial cancer operation, though we could not verify the duration of medication use through prescription data.

We observed heterogeneity among the medication groups, as multiple medication use is common in patients with T2D, which is consistent with the previous retrospective clinical studies. The metformin non-user group included 22 patients who also used insulin alongside metformin. Although the

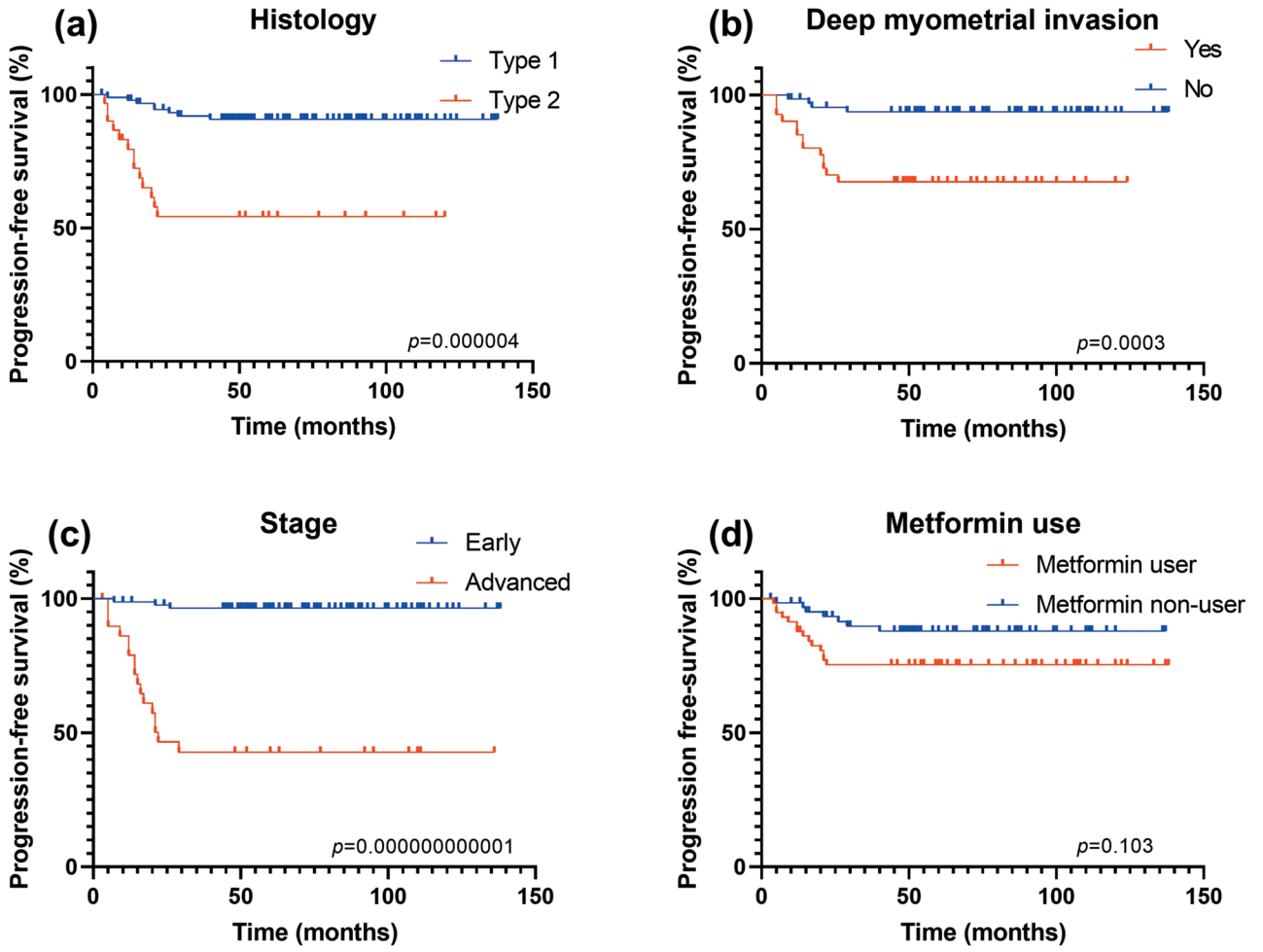

Figure 3. *Kaplan-Meier curves demonstrate associations between (a) histology, (b) myometrial invasion (c) stage or (d) metformin use and progression-free survival.*

Table III. *The results of multivariate analysis. Significant p-Values are given in bold.*

	Overall survival			Progression-free survival		
	Hazard ratio	95% Confidence interval	*p*-Value	Hazard ratio	95% Confidence interval	*p*-Value
Stage	2.279	1.038-5.006	**0.04**	16.001	4.225-60.602	**0.00004**
Histology	3.516	1.688-7.322	**0.001**	2.357	0.734-7.566	0.15
Age at diagnosis	1.058	1.012-1.106	**0.013**	0.996	0.937-1.057	0.886
Metformin use	0.858	0.411-1.794	0.685	1.081	0.357-3.266	0.891

majority of previous epidemiological studies have classified patients as metformin ever-users or metformin never-users, we decided to categorise those patients who used metformin along with insulin into the metformin non-user group. In a Danish study, insulin initiation was a stronger predictor of death from other causes in many types of cancer itself (34). Also, in one of our previous studies, insulin use was associated with increased mortality from other causes than endometrial cancer (30). Furthermore, mortality from cancer is increased in patients who use metformin or sulphonylureas with

subsequent insulin treatment compared with patients not using insulin (35). Insulin is not only an important regulator of cell metabolism but also a growth factor for cancer cells *in vitro via* its receptor and insulin-like-growth factor 1 receptor (36).

The current knowledge and data from the Cancer Genome Atlas (TCGA) define four clinically distinct endometrial cancer types based on their p53 mutational burden, exonuclease domain of the DNA polymerase epsilon (POLE) mutations and microsatellite instability (37, 38). We were unable to recategorize our endometrial cancer cases according to TCGA. Lack of information on p53 mutation status in our study is probably a minor limitation since most grade 3 endometrioid carcinomas with p53 mutation would anyway have a poor prognosis and belong to the type 2 cancer group. POLE mutation analysis is not yet available in every-day cancer diagnostics, so these rare cancers with p53 mutation but better prognosis are not currently identified. Microsatellite instability (MSI) status was not analysed in the primary diagnostics in our patient group.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

EU and RA collected the data; AA revised the histological cancer data/properties; EU performed statistical analysis and wrote the original draft of the manuscript; EU, RA, PK, UP, and AA revised subsequent drafts and approved the final draft for submission. All Authors have read and agreed to the published version of the manuscript.

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